DETAILED ACTION

Receipt of Amendments/Remarks filed on August 19 2011 is acknowledged. Claims 8, 10-11, 16, 19-20 and 35 were/stand cancelled. Claims 1, 5-7, 12-13, 17-18, 22-25, 27-31 and 36 were amended. Claims 1-7, 9, 12-15, 17-18, 21-34 and 36 are pending. Claims 33-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (species), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 22 2011. Claims 1-7, 9, 12-15, 17-18, 21-32 and 36 are directed to the elected invention.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Modified Rejections Based on amendments in the reply filed on August 19 2011

Claims 1-7, 9, 12, 17-18, 28-30 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (WO 01121184, cited on PTO Form 1449) in view of Smith (Lancet, 1992, cited in the Office action mailed on 4/29/11) and Tikka et al. (J. Neurochemistry, 2001, cited on PTO Form 1449).

Applicant Claims

The instant application claims a method of reducing motorneuron loss associated with amyotrophic lateral sclerosis (ALS), the method comprising administering to the subject for a time period exceeding three weeks a therapeutic amount of ceftriaxone or a salt thereof which is sufficient to reduce motorneuron loss.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Koppel is directed to neurotherapeutic compositions and method. Claimed is a method of treating a human patient afflicted with a condition characterized at least in part by abnormal extracellular glutamate concentration in the brain or other nervous tissue. Claimed compounds include beta-lactams such as cephalosporins (claims 33-34 and 36). The condition claimed includes ALS (claim 39). Beta-lactam antibiotics taught include ceftriaxone and ceftriaxone sodium (page 38, lines 19-20). Parenteral dosages of the beta-lactams can range from about 1 to about 80 mg per dose (page 42, lines 11-12). Parenteral routes of administration include intramuscular and intravenous (page 45, lines 16-20). It is taught that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state (page 46, lines 12-23). The plasma concentration is around 50 pM (page 79 line 2).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Koppel suggest that ceftriaxone and ceftriaxone sodium can be utilized to treat ALS, Koppel does not exemplify this method of treatment. However, this deficiency is cured by Smith.

Smith teaches reports that ceftriaxone can be utilized to improve ALS (right column).

Koppel does not expressly state reducing motorneuron loss. However, this deficiency is cure by Tikka et al.

Tikka et al. teach that tetracycline derivatives and ceftriaxone protect neurons against apoptosis (i.e. motorneuron loss). It is taught that programmed cell death (apoptosis) is an important mechanism of neuronal death in both acute and slowly progressing brain diseases such as amyotrophic lateral sclerosis (ALS) (page 1409, left column, first paragraph). Tikka et al. show that administration of ceftriaxone significantly reduces lactate dehydrogenase release. Lactate dehydrogenase release is indicative of cell death (page 141reducet column, first paragraph under results). Tikka et al. concludes that ceftriaxone provides significant protection of neuronal apoptosis (page 1412, left column, first paragraph under discussion). The results show that ceftriaxone has protective functions unrelated to its antimicrobial action (page 1413, left column, first column).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel, Smith and Tikka et al. and utilize ceftriaxone reduce motorneuron loss in ALS patients. One of ordinary skill in the art would have been motivated to utilize ceftriaxone to treat ALS as Koppel suggest this use and one of ordinary skill in the art would have been motivated to choose ceftriaxone out of all the beta-lactam antibiotics taught by Koppel as Smith recognizes that it can improve ALS. One of ordinary skill in the art would have been motivated to administer ceftriaxone to reduce motorneuron loss associated with ALS as ALS is associated with

neuronal cell death and ceftriaxone has been shown by Tikka et al. to be protective against neuronal cell death. Therefore, one of ordinary skill in the art would have been motivated to treat ALS by reducing motorneuron loss via the administration of ceftriaxone based on the teachings of Koppel, Smith and Tikka et al.

Regarding the claimed amount of ceftriaxone compound, Koppel teach overlapping amounts. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. **See MPEP 2144.05 [R-5].**

Regarding the claimed length of administration, Koppel teaches that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state. Therefore, the length of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art to utilize a kit for the administration of ceftriaxone. One of ordinary skill in the art would have been motivated to utilize a kit in order to package and ship the formulation as well as to provide instructions for a consumer/provider on how to utilize the product. "Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *In re Ngai*, 367 F.3d 1336, 70 USPQ2d 1862 (Fed. Cir. 2004). **See MPEP 2112.01 [R-3].** The applicant has not indicated that the instructions indicate some unobvious functional relationship between the product and the instructions.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel in view of Smith and Tikka et al. and in further view of Khanna et al. (US Patent No. 5869649).

Applicant Claims

The instant application claims the beta-lactam is ceftriaxone disodium salt, sesquarterhydrate.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel, Tikka et al. and Smith are set forth above. Specifically, Koppel teaches that beta-lactam compounds such as ceftriaxone sodium can be utilized

to treat ALS. Smith confirms that administration of ceftriaxone has been shown to improve ALS patients. Tikka et al. teach that administration of ceftriaxone protects neurons against apoptosis.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Koppel does not teach the ceftriaxone sodium is ceftriaxone disodium slat sesquarterhydrate. However, this deficiency is cured by Khanna et al.

Khanna et al. is directed to the preparation of cephalosporin antibiotics namely ceftriaxone sodium (abstract). Formation of ceftriaxone sodium results in the disodium salt hemiheptahydrate (example 3).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel, Smith, Tikka et al. and Khanna et al. and utilize ceftriaxone disodium hemiheptahydrate (sesquarterhydrate) as Koppel teaches that ceftriaxone sodium can be utilized and Khanna et al. teaches that the formation of ceftriaxone sodium results in the formation of ceftriaxone disodium salt hemiheptahydrate.

Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel in view Smith and Tikka et al. and in further view of Miller et al. (Neurology, 1996, cited on PTO Form 1449).

Applicant Claims

The instant application claims administering riluzole in combination with the beta-lactam compound.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel, Tikka et al. and Smith are set forth above. Specifically, Koppel teaches that beta-lactam compounds such as ceftriaxone sodium can be utilized to treat ALS. Smith confirms that administration of ceftriaxone has been shown to improve ALS patients. Tikka et al. teach that administration of ceftriaxone protects neurons against apoptosis.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Koppel does not teach administering ceftriaxone in combination with riluzole. However, this deficiency is cured by Miller et al.

Miller et al. teach that riluzole is the first drug approved by the FDA for use in treating ALS (abstract).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel, Smith, Tikka et al. and Miller et al. and utilize riluzole in combination with ceftriaxone. One of ordinary skill in the art would have been motivated to utilize this combination as both are taught as drugs useful for the treatment of ALS. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose,

in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Claims 14-15 and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel in view Smith and Tikka et al. and in further view of Bristol et al. (Annals of Neurology, 1996, cited on PTO Form 1449).

Applicant Claims

The instant application claims EAAT2 protein expression is increased. The instant application claims determining of level of EAAT expression in the subject.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel, Tikka et al. and Smith are set forth above. Specifically, Koppel teaches that beta-lactam compounds such as ceftriaxone sodium can be utilized to treat ALS. Smith confirms that administration of ceftriaxone has been shown to improve ALS patients. Tikka et al. teach that administration of ceftriaxone protects neurons against apoptosis.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Koppel teach treating diseases associated with abnormal extracellular glutamate concentration, Koppel does not teach measuring EAAT expression or increasing EAAT2 expression. However, these deficiencies are cured by Bristol et al.

Bristol et al. is directed to glutamate transporter gene expression in amyotrophic lateral sclerosis motor cortex. Defects in functional glutamate transport have been identified in ALS brain and spinal cord. Tissue culture studies mimicking the loss of glutamate transporter suggests that defective glutamate transport in ALS could account for, or at least contribute to, motor neuron degeneration (page 676, left column). Three glutamate transporter subtypes where cloned including the human equivalents EAAT1, EAAT2 and EAAT3. The changes in glutamate transport in ALS were found to be specific for the GLT-1 subtype (EAAT2) as revealed by a large loss of the transporter protein (right column, first paragraph). It is postulated that the loss of GLT-1 protein (EAAT2) could account for elevated CSF levels of glutamate and could propagate motor neuron degeneration in ALS (page 678, last paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel, Smith, Tikka et al. and Bristol et al. and measure EAAT expression before and after administration of the beta-lactam compound. One of ordinary skill in the art would have been motivated to measure EAAT expression before administration to aid in diagnosing ALS as Bristol teaches that low levels of EAAT protein expression are shown in ALS patients. One of ordinary skill in the art would have been motivated to measure the levels of EAAT expression to determine if correction to glutamate transport is seen. Since both Koppel and Bristol et al. recognize that ALS is associated with defective glutamate transport, it would have

been obvious to one of ordinary skill in the art to monitor EAAT protein expression during the course of therapy.

Regarding the claimed level of EAAT2 production, although Koppel does not disclose all the characteristics and properties of the composition disclosed in the present claims, based on the substantially identical process using identical components (same drug (beta-lactam) in the same or overlapping amount), the Examiner has a reasonable basis to believe that the properties claimed in the present invention are necessarily present in the composition disclosed by Koppel. Because the PTO has no means to conduct analytical experiments, the burden of proof is shifted to the Applicant to prove that the properties are not inherent. ""[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." MPEP § 2112, I.

Response to Arguments

Applicants argue that (1) Koppel is directed to methods for modulating behavior comprising administering clavulanic acid. Therefore, Koppel fails to treat or suggest method for reducing motor neuron loss. Applicants argue that (2) Smith is inoperative because the author later admits that the original report was inaccurate.

Applicants' arguments filed August 19 2011 have been fully considered but they are not persuasive.

Regarding applicants' first argument, Koppel claims a method of treating human patient afflicted with a condition. A specific condition claimed is ALS (claim 39). Ceftriaxone is a specific drug taught by Koppel. While Koppel does not exemplify ceftriaxone administration for treating ALS, Koppel clearly suggest this administration. The examiner recognizes that Koppel does not expressly teach administration of ceftriaxone reduces motorneuron loss, Koppel does suggest administration to the same patient population (i.e. patients with ALS). Since Smith recognizes that ceftriaxone is beneficial in treating ALS, the examiner maintains administration of ceftriaxone to patients with ALS is obvious. Tikka et al. expressly show that administration of ceftriaxone protects against neuronal loss. Therefore, the examiner maintains that administration of ceftriaxone to patients with ALS is obvious and administration of this drug to these patients would necessarily reduce motorneuron loss.

Regarding applicants' second argument, while the examiner could not find this Smith reference submitted with the file, the examiner did go out and get this reference. Smith is not a teaching away from utilizing ceftriaxone in treating ALS. What Smith states is that administration of ceftriaxone to a man with amyotrophic lateral sclerosis caused striking improvement to that man. However, the treatment was stopped for two weeks because acute pancreatitis developed. Since improvement was clearly seen at one point with administration of ceftriaxone, it would have been obvious to one of ordinary skill in the art to administer that compound, which is taught by Koppel, in the

method claimed by Koppel. Since as taught by Tikka et al., ceftriaxone protects against neuronal loss, it would have been obvious to administer the compound in diseases wherein neuronal loss is associated such as ALS.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher
Examiner
Art Unit 1616

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616